U.S. Serial No. 09/284,424
Group Art Unit No. 1623

REMARKS

Claims 1 – 8, 10 – 30, 34, 38 – 41, and 44 – 51 were pending in the instant application. Claims 1, 17, 18, 20 and 34 have been amended, and new claims claim 52 – 54 have been added. Accordingly, claims 1 – 8, 10 – 30, 34, 38 – 41, and 44 – 54 will be pending in the application upon entry of the claim amendments and additions presented herein.

The claims have been amended to correct certain typographical errors. Specifically, in claim 1, the substituent on page 141, line 4, clearly should contain a carbonyl group, and the "O" has therefore been changed to a "C"; on page 139, the substituent shown on line 15 is identical to that shown on page 140, line 25, such that the "S" atom shown in the substituent on page 139, line 15, has been changed to an "O" atom; and on page 144, line 10, a pentavalent carbon is shown, such that the "$(CH_2)_n$" on line 12 was moved to the right so it is now shown properly bonded to the CH adjacent to the carbonyl. Likewise, claim 18 has been amended to refer to "R^3" rather than "R^2". Further, claim 1 and, likewise, claims 17, 18, 20 and 34, have been amended to delete any reference to heterocycle or heteroaryl, so that the claims no longer read on non-elected subject matter. In addition, the proviso appearing at the end of claim 1 has been removed and replaced by a recitation excluding the 57 specific compounds disclosed by the prior art.

Support for the claim amendments can be found throughout the specification and claims as originally filed. In particular, support for the amendments to claim 1 can be found at least, for example, in the 194 working examples disclosed on pages 60-135 of the specification. Support for new claims 52 – 54 can be found in claim 1 as filed, as well as in the specification beginning at page 40, line 7. No new matter has been added.

In particular, support for the recitation of R^7 in amended claim 1 may be found in exemplified compounds 9b, 9e, 9y, and 9z which illustrate various alkylthioethers, and in compounds 9a, 9q, 9r, 9s, 9cc, and 9ee which illustrate various alkylsulfonates. Likewise, the dihydronaphthyl group recited in the definition of R^2 in amended claim 1 is supported by compound 1ff in the specification as filed which contains such a dihydronaphthyl group. Similarly, the fluorenyl group recited in the definition of R^2 in amended claim 1 is supported by the specification as filed by compound 1ff which contains such a fluorenyl group. Additionally,

the recitation of an alkylsulfonamide group in the definition of J in amended claim 1 is supported by compound 3d in the specification as filed.

Amendment of the claims herein should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, or in any previous Office Action, and was done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or one or more or subsequent applications.

Attached hereto as Appendix A, captioned "**Version with markings to show changes made**", is a marked-up version of the changes made to the claims by the amendments presented herein.

In addition, page 76 of the specification has been amended to correct a typographic error in the name of the title compound of Example 2e. Attached hereto as Appendix B, captioned "**Version with markings to show changes made**", is a marked-up version of page 76 to show the change made to the specification; *i.e.*, the change from "-ethylsulfanylamino)" to "-ethylsulfonylamino)" in the name of the title compound of Example 2e. Also attached is a replacement page 76 in clean form.

Claim Rejections - 35 U.S.C. §112

Rejection of Claim 1 Under 35 U.S.C. §112, First Paragraph

In the final Office Action dated February 22, 2001, claim 1 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that Applicants have not pointed out where in the specification there is support, explicit or implicit, for each and every limitation in the claim as amended. In particular, the proviso, added by amendment to claim 1 in Applicants' response mailed April 25, 2000, is believed to be at issue.

Applicants respectfully disagree, and submit that the proviso presented in the April 25, 2000 response is supported by the specification. However, without acquiescing to the rejection and in order to expedite prosecution, claim 1 has been amended wherein the proviso has been replaced by an exclusion of 57 compounds disclosed in the various prior art references.

Support for the amendment to claim 1 can be found in the 194 compounds disclosed in the specification at pages 60-135, which were synthesized and tested for biological activity. By virtue of the disclosure of these compounds, the specification describes the subgenus created by the exclusion of the 57 prior art compounds. This subgenus embraces all of these 194 compounds. Moreover, the significant amount of physical and biological data set forth in the specification surely demonstrate that Applicants were in possession of the claimed invention at the time of filing.

Indeed, the present amendment to claim 1 is clearly permitted under *In re Johnson*, which states that an applicant is permitted to narrow the scope of pending claims by merely excising the invention of another to which the applicant is not entitled. *In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977). To hold otherwise would "let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed." *Id.* at 1018.

In *Johnson*, the C.C.P.A. permitted a patent applicant to enter a proviso to the claims in order to overcome a prior art rejection, even though that proviso did not have *ipsis verbis* support in the specification. *Id. at 1013.* In particular, the Court indicated that in the applicant's application:

> "Fifty specific choices are mentioned for the E precursor compound, a broad *class* is identified as embracing suitable *choices* for the E' precursor compound, and twenty-six 'examples' are disclosed which detail fifteen species of polyarylene polyethers. Only fourteen of those species and twenty-three of the 'examples' are within the scope of the claims now on appeal. Two of the many choices for E and E' precursor compounds are deleted from the protection sought, because appellant is *claiming less* than the full scope of his disclosure.....It is for the inventor to decide what *bounds* of protection he will seek." [*Id.* at 1018; emphasis in original.]

Accordingly, the court held that "[w]e are convinced that the invention recited in claim 1 is 'disclosed in the manner provided by the first paragraph of Section 112' ". *Id.* at 1017.

In the present application, the situation is analogous to that in *In re Johnson*. The subgenus created by the amendment to claim 1 (as well as new claims 52 and 53) is supported in the specification by virtue of the 194 compounds specifically exemplified in the specification at

pp. 60-135. Further, the specification teaches that "n" in the claims may be 0 to 3. The proviso in claim 53 recites ranges for n that are disclosed in the specification. Likewise, the specification states in the paragraph starting at page 40, line 7, that an aryl group *may* be substituted with alkoxy, halogen, or trifluoromethyl, and therefore there is written support in the specification for the proviso "provided that the aryl group is not substituted with alkoxy, halogen, or trifluoromethyl" of claim 52. Applicants believe that claim 1 as amended overcomes the basis of this rejection, and that claims 1, 52 and 53 are consistent with *In re Johnson*. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Claim Rejections - 35 U.S.C. §103

Rejection of Claims 1-8, 10-30, 34, 38-41 and 44-51 under 35 U.S.C. §103(a)

In the final Office Action dated February 22, 2001, claims 1-8, 10-30, 34, 38-41, and 44-51 are rejected under 35 U.S.C. §103(a) as unpatentable over Prasad *et al.* in view of Mjalli *et al.*, Dolle *et al.* and Chapman. The Examiner has rejected the claims for the reasons set forth in the Office Action dated July 5, 2000 (Paper No. 8), asserting that a proper *prima facie* case of obviousness has been established. Applicants respectfully disagree and traverse the rejection for the reasons of record set forth in their response filed December 6, 2000 and in their response filed July 27, 2001, and reiterate those reasons here. Applicants further traverse the rejection for the additional reasons as follows.

In order to establish a *prima facie* showing of obviousness, the Examiner must show the following three elements: suggestion or motivation to combine the cited references; reasonable expectation of success; and the combination of references must teach all the limitations of the claim at issue. Failure to show any one of the foregoing negates a *prima facie* showing. The Examiner takes the position that all three elements have been established. However, Applicants submit that the Examiner has failed to establish all three elements.

Suggestion or motivation to combine references: The Examiner alleges that Prasad *et al.* teach the structural requirements for rational design of ICE inhibitors in which the most potent ones are aspartate α-(arylacyl)oxymethyl ketones with zero (only a protecting group) to three (natural/unnatural, protected/non-protected) amino acids attached through the aspartate amine moiety; *i.e.*, the variable R^1 in the formula of claim 1. Applicants disagree.

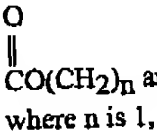
Although the cited references teach specific ICE inhibitors, none of the references explicitly or implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the cited references, alone or in combination, neither teach nor suggest that a particular first element of the ICE inhibitors of one reference should be combined with a particular second element of the ICE inhibitors of another reference to arrive at the compounds recited by the instant claims. Prasad *et al.* and Dolle *et al.* only demonstrate the an aspartic acid core may be important, but fail to provide any teaching selection of specific substituents at either end of the core to arrive as the particular compounds of the present invention. Nor has the Examiner demonstrated how the teachings of Prasad *et al.* or Dolle *et al.* may be modified, or combined with the other references cited in the Office Action, to arrive at the present invention.

In particular, Prasad *et al.* do not teach or suggest modifying R^2 of the instant invention, nor do they suggest modifying R^1 to include other substituents disclosed in the instant invention. Indeed, with respect to the Applicants' invention, none of the specific compounds disclosed by Prasad *et al.* or Dolle et al. is within the scope of the claims as amended. Compound 1 of Prasad *et al.* (*see* page 316) is specifically excluded from claim 1. Likewise, in order to fall within the scope of claim 52, R^2 would have to be a chlorine-substituted aryl group, *i.e.* $-(CRR)_n-$(substituted-aryl). However, such a substituent is excluded by the text "provided that the aryl group is not substituted with alkoxy, halogen, or trifluoromethyl" in claim 52. Also, claims 53 and 54 do not permit $-(CRR)_n-$(substituted-aryl) as an R^2 group, and therefore compound 1 of Prasad *et al.* is not within the scope of these claims.

In fact, *all* of the compounds of Prasad *et al.* and Dolle *et al.* with an aspartic acid core have such a substituted aryl group. Consequently, one of ordinary skill in the art would likely consider a substituted aryl R^2 group to be a critical component of the Prasad *et al.* and Dolle *et al.* disclosures, and therefore one would not expect to be able to alter that component with success. Accordingly, one of ordinary skill in the art would not consider these two references in attempting to make a combination that would suggest the instant invention. Thus, the requisite motivation to combine is lacking.

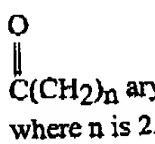
In a similar manner, the compounds disclosed in Chapman *et al.* and Mjalli *et al.* are not within the scope of the present invention, nor is the invention obvious over these references. Chapman *et al.* and Mjalli *et al.*, like Prasad *et al.* and Dolle *et al.*, disclose compounds having an R^2 group corresponding to -$(CRR)_n$-(substituted-aryl), and those compounds are similarly not within the scope of the present invention. Nor is there any explanation in the Office Action of why one skilled in the art would be motivated to modify the teachings of Chapman *et al.* and Mjalli *et al.* to arrive at the present invention.

Chapman *et al.* and Mjalli *et al.* also disclose aspartic acid-containing compounds having groups corresponding to the following R^{5a} structures:



where n is 1,

and



where n is 2.

Neither of these R^{5a} moieties is permitted by claims 52 – 54. Claims 52 and 53 contain provisos which redefine the values which n may be, and claim 54 makes no provision for these R^{5a} moieties.

The Examiner argues that the "art-disclosed common core plus common utility would give the artisan sufficient suggestion and motivation to combine the references." Applicants respectfully disagree because the inhibition data disclosed in Prasad *et al.* is inconclusive. Although the ICE-inhibiting compounds of Prasad *et al.* contain an aspartate moiety, the substituents surrounding this aspartate greatly affect the ability of the compounds to inhibit ICE. The inhibition data presented in Prasad *et al.* are not conclusive (or suggestive of the present invention) because the inhibition data vary greatly (*see* Table 1, 2, and 3 therein) such that, based on these data, one of ordinary skill in the art would not know which substituents to select to arrive at the compounds of the invention. In light of this variability of inhibition data, one of

ordinary skill in the art would not be motivated to combine Prasad *et al.* with any of the other references to arrive at the instant invention.

It is well settled that the motivation to combine references must come from the cited references themselves, and cannot be derived from Applicants' teachings. However, it is clear from the foregoing that the alleged motivation to combine presented in the Office Action is nothing more than a hindsight reconstruction of the invention based solely Applicant's own teachings.

Reasonable expectation of success: The Examiner states that although there is no perfect predictability in drug design, all of the cited references teach potent ICE inhibitors with the same compound core, with a variety of modifications on either end, corresponding to R^1 and R^2 in formula I. The Examiner goes on to conclude that based on the overlapping sets of compounds and teachings with regard to desired structural elements, one of ordinary skill in the art would have a reasonable expectation of success. Applicants respectfully disagree.

First, as discussed in detail above, none of the references, alone or in combination, provide any guidance whatsoever as to which structural elements to choose to arrive at the claimed compounds. Second, *all* of the specific compounds of Prasad *et al.* and Dolle *et al.* with an aspartic acid core have a substituted aryl group, and therefore are excluded from the claims as amended herein. Consequently, one of ordinary skill in the art would likely consider a substituted aryl R^2 group to be a critical component of the Prasad *et al.* and Dolle *et al.* disclosures, and therefore one would not reasonably expect to be able to alter that component and still obtain compounds with acceptable ICE inhibitory activity. Third, the inhibition data disclosed in Prasad *et al.* is inconclusive. Although the ICE-inhibiting compounds of Prasad *et al.* contain an aspartate moiety, the substituents surrounding this aspartate greatly affect the ability of the compounds to inhibit ICE. The inhibition data presented in Prasad *et al.* are not conclusive (or suggestive of the present invention) because the inhibition data vary greatly (*see* Table 1, 2, and 3 therein). In light of this variability of inhibition data, one of ordinary skill in the art would not have been led to conclude that he/she would have a reasonable expectation of success in developing ICE inhibitors based on the claimed compounds.

All limitations must be taught: The Examiner asserts that the art teaches zero to three amino acids at the R1 position of formula I, and that substitution at this position with any

common amino acid protecting group would be an obvious variation. However, to meet the all limitations criterion, the combination of references must teach each and every element of the claim at issue such that the combination of references puts the artisan of ordinary skill in possession of the invention as claimed. The position in the Office Action that substitution with any common amino acid protecting group would be an obvious variation is not relevant. The fact is that the combination of references must specifically disclose the substituents recited by the claims at issue. As discussed above, that is just not the case.

Allowable Subject Matter

On page 6 of the Office Action dated October 25, 1999 (Paper No. 4), the Examiner indicated that claims 3, 8, 12-15, 17, 19, and 20-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and excluding any material drawn to the non-elected subject matter. Inasmuch as the these claims are still pending, Applicants respectfully request that the Examiner confirm that claims 3, 8, 12-15, 17, 19, and 20-23 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and excluding any material drawn to the non-elected subject matter.

Duty of Disclosure

Prior to the filing of the instant CPA, Applicants filed a Supplemental Information Disclosure Statement (SIDS) on September 19, 2001. The SIDS was filed for the purpose of making of record those references that were cited in the International Search Report of the corresponding PCT international application, and those that were cited in the Examination Report issued by the Norwegian Patent Office in the corresponding Norwegian patent application.

The undersigned wishes to invite the Examiner's attention to certain errors in the SIDS, errors that occurred through oversight and without any deceptive intent on the part of the undersigned. First, the International Search Report, and the references cited therein, that were submitted in the SIDS were from international application no. PCT/US00/25468, filed on September 19, 2000. However, this international application does not correspond to the instant

application. The international application that does correspond to the instant application is international application no. PCT/US97/18514, filed on October 9, 1997. Thus, international application no. PCT/US00/25468, filed on September 19, 2000, the International Search Report therefor, and the references cited therein, are not relevant to the instant application.

Moreover, the International Search Report and the references cited therein for international application no. PCT/US97/18514, filed on October 9, 1997, were already made of record, and considered by the Examiner, by virtue of the Information Disclosure Statement (IDS) filed July 26, 1999 in the instant application. Furthermore, the references cited in the Norwegian Examination Report and reported in the September 19, 2001 SIDS are the same references that were reported in the June 26, 1999 IDS and, therefore, were already made of record and considered by the Examiner.

Finally, the certification under 37 C.F.R. §1.97(e)(2) set forth on page 2 of the September 19, 2001 SIDS was erroneous. The certification was included in the SIDS through an oversight and in error without deceptive intent.

Accordingly, the September 19, 2001 SIDS is completely superfluous and should be ignored in its entirety.

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CONCLUSION

In view of foregoing, entry of the amendments and remarks presented herein, favorable reconsideration and withdrawal of all rejections, and allowance of this applications with all the claims that will be pending are respectfully solicited. If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: Peter C. Lauro

Peter C. Lauro, Esq.
Registration No. 32,360
Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

Dated: July 30, 2002

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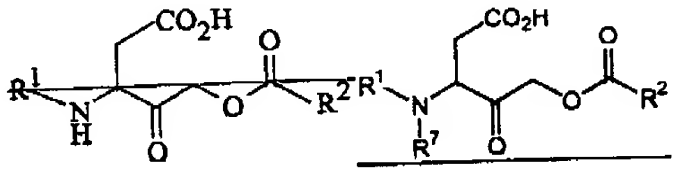
APPENDIX A

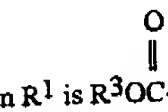
VERSION WITH MARKINGS TO SHOW CHANGES MADE

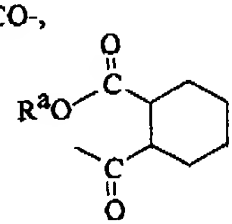
1. (Thrice Amended) A compound of the Formula I



I

wherein R^1 is R^3OC-,
R^3CO-,
R^3SO_2-,





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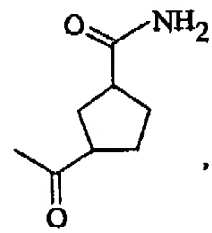

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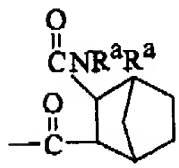

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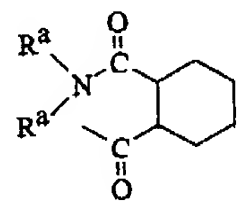

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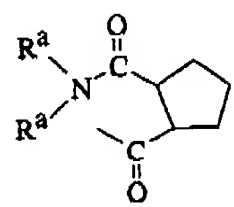

;

each R^a is independently hydrogen, C_1-C_6 alkyl, or -$(CH_2)_n$ aryl;

R^2 is -$(CRR)_n$-aryl,
-$(CRR)_n$-X-aryl,
~~-$(CRR)_n$-heteroaryl,~~

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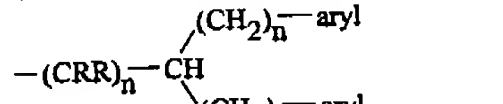
~~$-(CRR)_n$-X-heteroaryl,~~
~~$-(CRR)_n$-(substituted-heteroaryl),~~
$-(CRR)_n$-(substituted-aryl),
$-(CRR)_n$-X-(substituted-aryl),
$-(CRR)_n$-aryl-aryl,
~~$-(CRR)_n$-aryl-heteroaryl,~~
$-(CRR)_n$-aryl-$(CH_2)_n$-aryl,
$-(CRR)_n$-CH(aryl)$_2$,
$-(CRR)_n$-cycloalkyl,
$-(CRR)_n$-X-cycloalkyl,
~~$-(CRR)_n$-heterocycle,~~
~~$-(CRR)_n$-X-heterocycle,~~
~~$-(CRR)_n$-substituted heterocycle,~~



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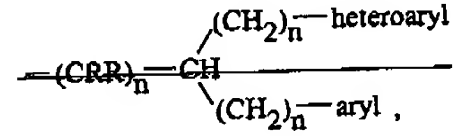

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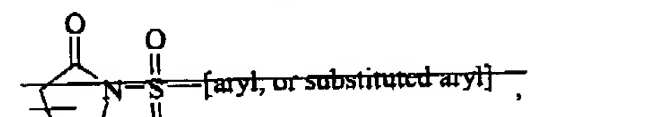

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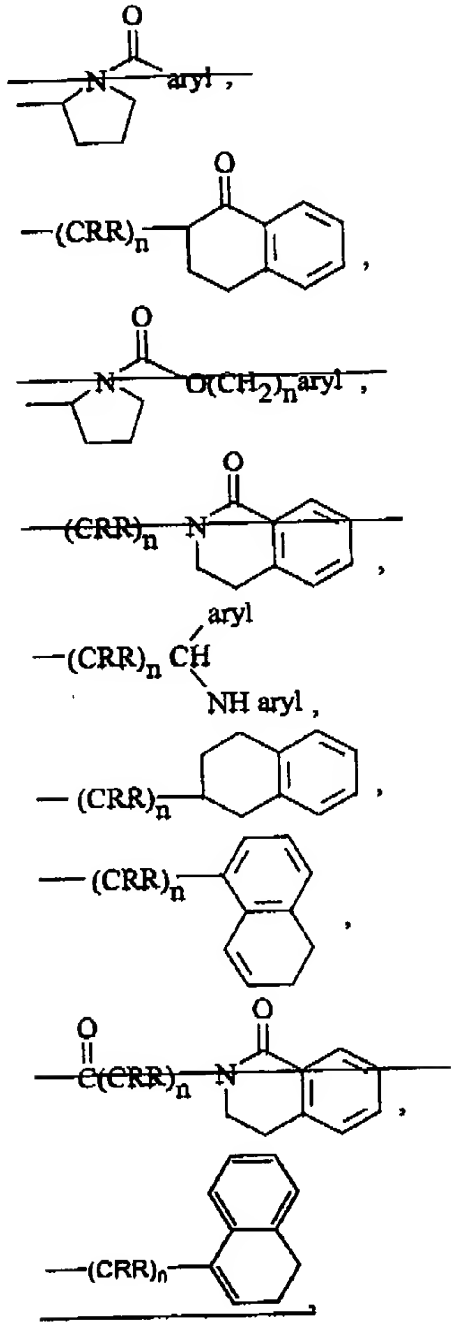

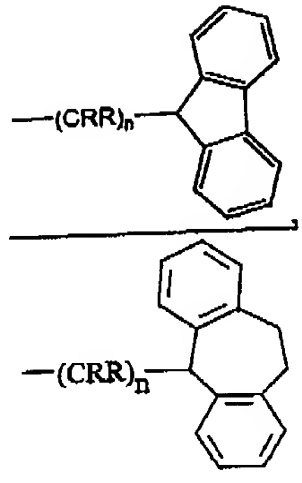

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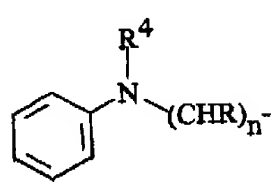

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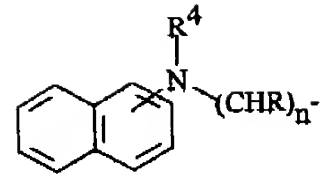

;

each R is independently hydrogen, C_1-C_6 alkyl, halogen or hydroxy;
X is O or S;
R^3 is C_1-C_6 alkyl,
aryl,
~~heteroaryl,~~
-$(CHR)_n$-aryl,
~~-$(CHR)_n$-heteroaryl,~~
~~-$(CHR)_n$-substituted heteroaryl,~~
-$(CHR)_n$-substituted aryl,

-$(CRR)_n$$COR^a$,
-$(CRR)_n$$SO(CH_2)_n$-aryl,
cycloalkyl,
substituted cycloalkyl,
~~heterocycle,~~
~~substituted heterocycle,~~

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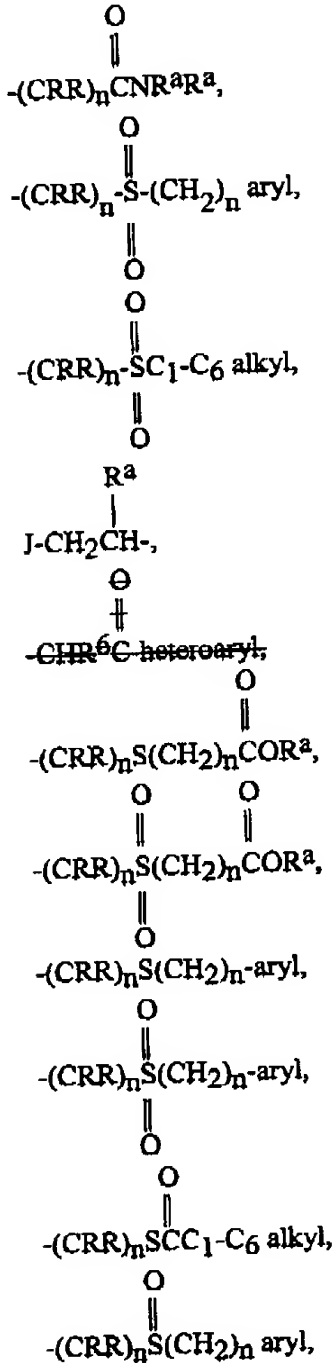

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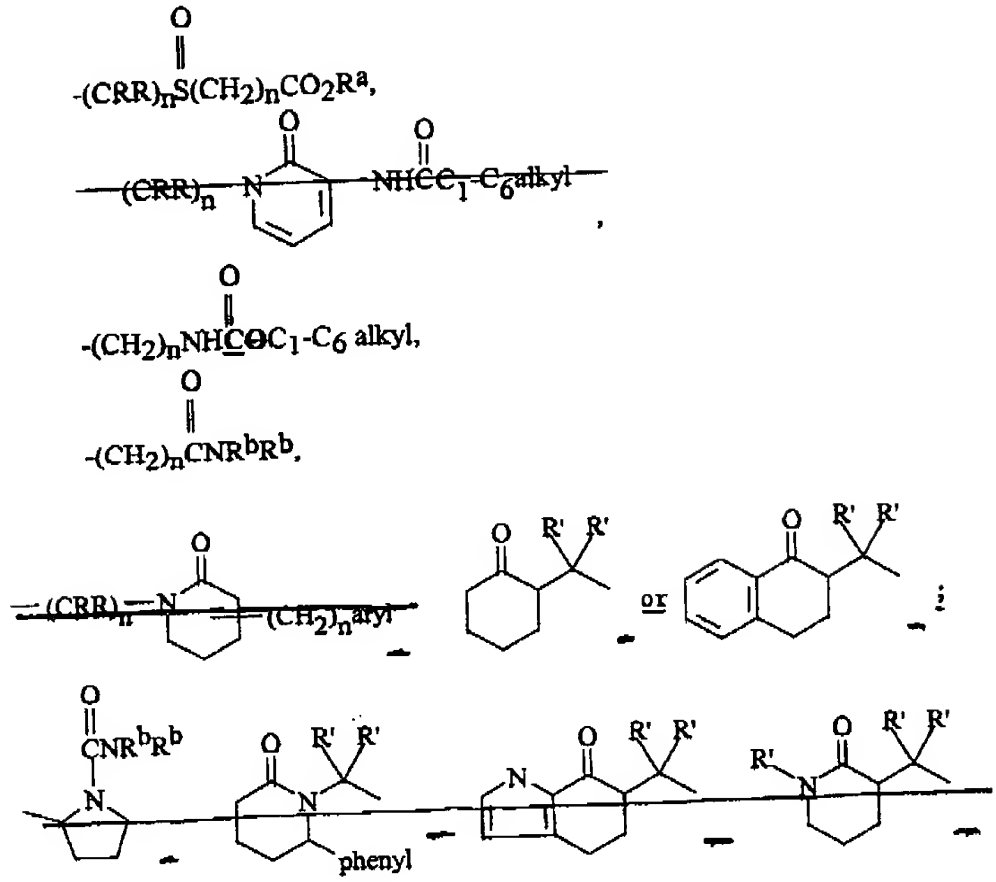
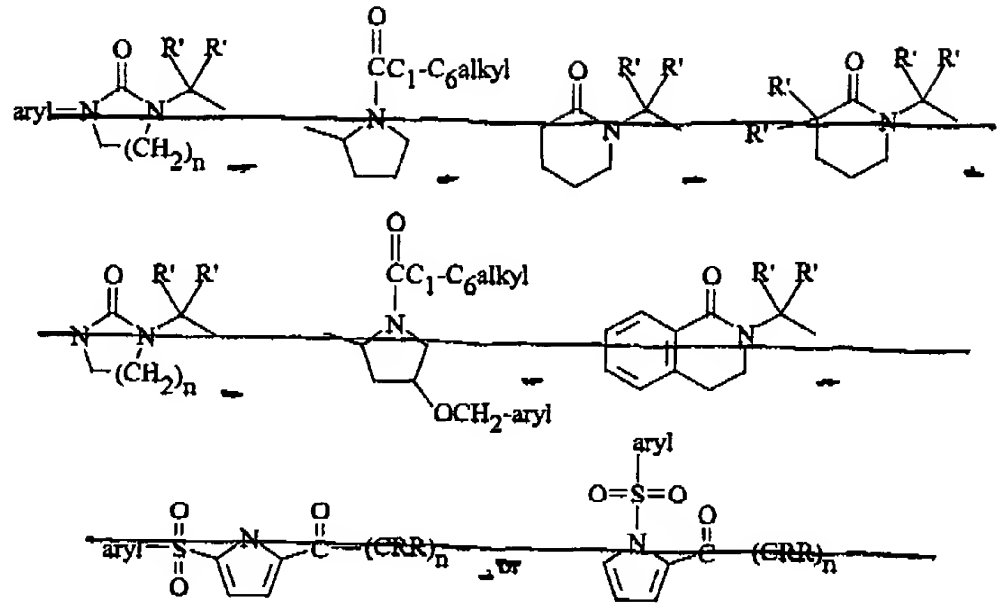
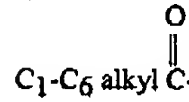


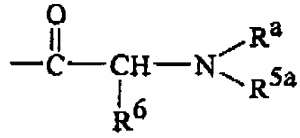


each R' is independently C_1-C_6 alkyl,
C_1-C_6 alkylaryl,
aryl, or
hydrogen;
each J is independently
-NH-SO_2-(C_1-C_6-alkyl),
$-CO_2R^b$,
$-CONR^bR^b$,
$-SO_2NR^bR^b$, or
$-SO_2R^b$;
each R^b is independently hydrogen, C_1-C_6 alkyl, aryl, substituted aryl~~,~~ arylalkyl, ~~heteroarylalkyl, or~~ substituted arylalkyl~~, or substituted heteroarylalkyl~~;
R^4 is hydrogen,
C_1-C_6 alkyl,

-phenyl, or



R^5 is C_1-C_6 alkyl-CO-,
-$(CH_2)_n$ aryl,
C_1-C_6-alkyl$\overset{O}{\overset{\|}{O}}C$-,
C_1-C_6-alkyl-X-$(CH_2)_n$CO,
C_1-C_6-alkyl-X-$(CH_2)_n\overset{O}{\overset{\|}{O}}C$-,
-$\overset{O}{\overset{\|}{C}}(CRR)_n$aryl,
-$\overset{O}{\overset{\|}{C}}NR^aR^a$,
-$\overset{O}{\overset{\|}{S}}C_1$-$C_6$ alkyl,
-$\overset{O}{\overset{\|}{O}}\overset{O}{\overset{\|}{C}}(CH_2)_nCNR^aR^a$,
-$\overset{O}{\overset{\|}{C}}O(CH_2)_n$ aryl,
-$\overset{O}{\overset{\|}{C}}O(CH_2)_n$ substituted aryl,
-$\overset{O}{\overset{\|}{C}}(CRR)_n\overset{O}{\overset{\|}{N}}HCO(CH_2)_n$-aryl,



-$(CH_2)_nX(CH_2)_n$-aryl, or
-C_1-C_6 alkyl X-C_1-C_6 alkyl aryl; ~~or~~

~~O O O~~
~~‖ ‖ ‖~~
~~-C-CH-NHC-CH-NHCC$_1$-C$_6$alkyl;~~
~~| |~~
~~$(CH_2)_n$ CH_2-heteroaryl~~
~~|~~
~~CO_2R^a~~

R^{5a} is

O
‖
CC_1-C_6 alkyl,

O
‖
-COC_1-C_6 alkyl,

~~O O~~
~~‖ ‖~~
~~-C-CH-NHCC$_1$-C$_6$-alkyl;~~
~~|~~
~~$(CH_2)_n$~~
~~|~~
~~aryl or substituted aryl;~~

O O
‖ ‖
-C-CH-NHCC$_1$-C$_6$ alkyl,
|
$(CH_2)_n$
|
aryl or substituted aryl,

O
‖
$CO(CH_2)_n$ aryl, or

O
‖
$C(CH_2)_n$ aryl~~, or~~

~~O O~~
~~‖ ‖~~
~~CCHNHCC$_1$-C$_6$-alkyl;~~
~~|~~
~~CH_2-heteroaryl~~

R^6 is hydrogen,

C_1-C_6 alkyl, -$(CH_2)_n$ aryl, -$(CH_2)_nCO_2R^a$, or hydroxyl substituted C_1-C_6 alkyl; ~~or imidazole substituted C_1-C_6-alkyl~~;

R^7 is hydrogen, –S–(C_1–C_6-alkyl), or –SO_2–(C_1–C_6-alkyl);

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, esters, amides, and prodrugs thereof;

~~and further provided that:~~

~~(a) when R^2 is aryl, substituted aryl, cycloalkyl, phenyl-phenyl-CH_2-, piperidino, heteroaryl or substituted heteroaryl; and R^1 is (R^5R^a)-N-CH-(R^6)-CO-, then R^a is not hydrogen when R^6 is a side chain of an amino acid;~~

~~R^5 is aryl-C(O)-; aryl-(CH_2)-O-C-(O)-NH-CH-(R)-C-(O)-;~~

~~where R is H or (C_1-C_6)alkyl or R^{5a}-NH-CH(R^6)-C(O)-;~~

~~where R^6 is a side chain of an amino acid and R^{5a} is an amino acid protecting group;~~

~~(b) when R^1 is R^3-O-C(O)- where R^3 is CH_2=CH-CH_2-, then R^2 is not $Ph(CH_2)_2$-, $PhO(CH_2)_2$-, trans-PhCH=CH- or cyclohexyl$(CH_2)_2$;~~

~~(c) when R^1 is (R^5R^a)N-CH(R^6)-CO-;~~

~~where R^6 is H, (C_1-C_6)alkyl, benzyl or hydroxyalkyl~~

~~R^a is H, (C_1-C_6)alkyl, phenyl or benzyl; and~~

~~R^5 is -C(O)-O-(C_1-C_6)alkyl, -C(O)-N(R^aR^a), -C(O)-(C_1-C_6)alkyl, -phenyl-O-(C_1-C_6)alkyl or -phenyl-$(CH_2)_{1-4}$-N(R^aR^a);~~

~~then R^3 is not a phenyl or naphthyl group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, CF_3, NO_2, (C_1-C_6)alkyloxy, -CO-(C_1-C_6)alkyl, -NR^a(C_1-C_6)alkyl, CON(R^aR^a), -SO_2N(R^aR^a), -SO_2-(C_1-C_6)alkyl, (C_1-C_6)alkyl, cycloalkyl and -O-$(CH_2)_{1-6}$-phenyl-O-(C_1-C_6)alkyl; and~~

~~(d) when R^1 is R^5-NH-CH(R^6)-C(O)-, where R^5 is R^{5a}-NH-CH(R^6)-C(O)- and R^{5a} is -C(O)-(C_1-C_6)alkyl or -C(O)-aryl, then R^2 is not mono-, di-, tri-, tetra- or penta-substituted phenyl or mono-, di, tri-substituted phenyl, 1-naphthyl, 9-anthracyl or 2-, 3- or 4-pyridyl.~~

excluding the following compounds:

N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbony-L-aspartic acid 2,6-ditrifluoromethyl benzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-(2-N-morpholinylethoxy)benzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-dimethoxybenzoyloxy methyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,-dichloro-3-(benzyloxy)benzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2-acetamido-6-chlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-difluorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 3-(N-butylsulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-sulfonamido benzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 3-(N-benzylsulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 3-(N-(2-aminoacetamidoyl)-sulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-(N-morpholinylsulfonamido)benzoyloxymethyl ketone;
N-Methoxycarbonyl-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(2-thienyl)carbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl glycine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-phenylalanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-histidine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-valine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(2-Furonyl)carbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(2-Furonyl)carbonyl-L-aspartic acid 2,6-dichloro-3-(N-morpholinylsulfonamido)benzoyloxymethyl ketone;
N-(3-Phenylpropionyl)-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(4-N,N-dimethylaminomethyl)benzoyl-L-aspartic acid 2,6-diclorobenz loxymethyl ketone;

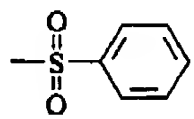
N-Benzyloxycarbonyl-D-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-L-histidine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-glycine -L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxy-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxy-D-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxy-L-alanine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxy-L-valine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxy-D-alanine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-(2,6-bistrifluoro methylbenzoyloxy) pentanoic acid;
N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-benzoyloxy pentanoic acid;
N-(N-Acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-(pentafluorobenz oyloxy) pentanoic acid;
3-Phenylpropionyl-L-valine-L-alanine-aspartic acid 2-phenylethylcarbonyloxymethyl ketone;
Adamantane-1-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
Acridine-9-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
1H-Indole-3-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
2-Methyl-imidazo[1,2-a]pyridine-3-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
2-Methoxy-3-methyl-quinoline-4-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
1,3-Dimethyl-1H-indole-2-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
9H-Xanthene-9-carboxylic acid 3-[2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-diphenylacetoxy-4-oxo-pentanoic acid;
2,6-Dichloro-benzoic acid 3-(5-benzyloxycarbonylamino-naphthalene-1-sulfonylamino)-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-{[2-(1-benzyloxycarbonylamino-2-methyl-propyl)-thiazole-4-carbonyl]-amino}-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-[2-(3-benzyloxycarbonylamino-phenyl)-propionylamino]-4-carboxy-2-oxo-butyl ester;

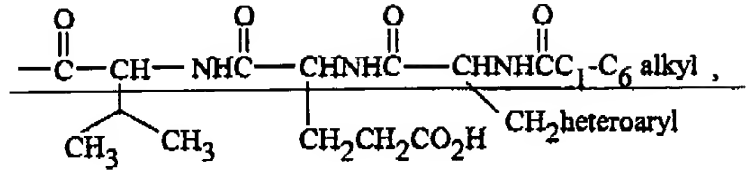
2,6-Dichloro-benzoic acid 3-[(5-benzyloxycarbonylamino-1H-indole-3-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-[2-(6-benzyloxycarbonyloxy-naphthalen-2-yl)-propionylamino]-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-(5-benzyloxycarbonylamino-naphthalene-1-sulfonylamino)-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-[(5-benzyloxycarbonylamino-naphthalene-1-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester;
2,6-Dichloro-benzoic acid 3-[(6-benzyloxycarbonylamino-5-oxo-octahydro-indolizine-3-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester; and
2,6-Dichloro-benzoic acid 3-[(4-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-carboxy-2-oxo-butyl ester.

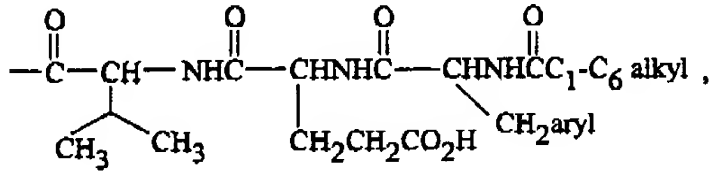
17. (Amended) A compound according to Claim 1 wherein each R^a is hydrogen; R^1 is benzyloxycarbonyl; R^2 is aryl-X$(CRR)_n$-, aryl-$(CRR)_n$-, ~~heteroaryl-$(CRR)_n$-~~, or cycloalkyl-$(CRR)_n$-; n is 1, 2, or 3; X is O or S; and R is hydrogen, methyl, or benzyl.

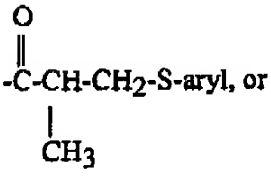
18. (Amended) A compound according to Claim 1 wherein each R^a is hydrogen;
R^1 is benzyloxycarbonyl; and
~~R^2~~**R^3** is -$(CH_2)_n$-naphthyl,
-$(CH_2)_n$-phenyl,
-$(CH_2)_n$-cycloalkyl,
-$(CH_2)_nO(CH_2)_n$-naphthyl,
-$(CH_2)_nO(CH_2)_n$-phenyl, or
-$(CH_2)_nS(CH_2)_n$-phenyl.

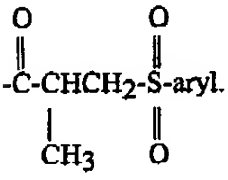
20. (Twice Amended) A compound in accordance with Claim 1 wherein each R^a is hydrogen; **and**
R^1 is benzyloxycarbonyl,











34. (Amended) The compounds:

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid;

~~(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(2-thiophene-2-yl-acetylamino)-pentanoic acid;~~

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(3-Carbamoyl-bicyclo[2.2.1]heptane-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Butyrylamino-5-(naphthalen-2-yl-acetoxy)-4-oxo-pentanoic acid;

3-Acetylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Carbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

[S-(R*,R*)]-3-(3-Acetylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

trans-3-[(3-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

APPENDIX B

VERSION WITH MARKINGS TO SHOW CHANGES MADE

EXAMPLE 2e

3-(2-Methanesulfonyl-1-methyl-~~ethylsulfanylamino)~~-ethylsulfonylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Analysis calculated for $C_{21}H_{25}NO_9S_2 \cdot 1.0\ H_2O$ (517.578):

C, 48.73; H, 5.26; N, 2.71.

Found: C, 48.90; H, 5.60; N, 2.78.

EXAMPLE 3

[S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To a solution at 0°C under nitrogen of N-acetyl alanine (0.176 g, 1.34 mmol), 3-amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester, hydrochloride (0.500 g, 1.22 mmol, Example 2, Step A), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.431 g, 1.34 mmol), 1-hydroxybenzotriazole (0.214 g, 1.58 mmol) in 15 mL of dichloromethane was added dropwise (via syringe) N,N-diisopropylethylamine (0.531 mL, 3.05 mmol). The solution was allowed to slowly warm to room temperature overnight. The solution was then dissolved in ethyl acetate and washed with 2× 5% citric acid solution, 2× saturated $NaHCO_3$, and 1× brine. The ethyl acetate extract was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel, 30% tetrahydrofuran-70% dichloromethane) to give [S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester as a light yellow thick oil.

Step B

A solution of [S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester (0.467 g, 0.96 mmol), and 7.5 mL of trifluoroacetic acid in 7.5 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated and chromatographed (silica gel, 94% dichloromethane-5% methanol-1% acetic acid)

EXAMPLE 2e

3-(2-Methanesulfonyl-1-methyl-ethylsulfonylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

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Found: C, 48.90; H, 5.60; N, 2.78.

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Step B

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